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Which albumin should we measure?

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Which albumin should we measure? Albumin circulates in the blood as a single homogeneous protein. During passage to the urine it can undergo configuration and digestive change, producing moieties not equally detected by the various methods currently routinely used for quantifying albuminuria. In normal urine, albumin is not the most common protein. In microalbuminuric states, detection techniques of great sensitively and specificity are required, looking for the whole molecule, immunoreactive moieties, peptide fragments, or all of these. We are unsure of the most accurate technique in terms of patient prognosis; accordingly, we must now ask "Which albumin should we measure?"

The recent interest in albumin in urine as a prognostic indicator in a wide variety of diseases warrants some reflection on what "albumin" means. Albumin is a very old word, derived from the Latin albus = white, referring to egg-white. Albumin is derived from the same root, although conventionally used to refer to pure proteins. Hence, albumins are a group of proteins characterized by heat coagulability and stability in dilute salt solutions [1].

Albuminuria

Around the turn of the 18th century many wrote of coagulable urine, including William Wells (1757–1817), who correctly concluded that the coagulable material was derived from the blood [2]. Richard Bright linked kidney disease, dropsy, and albuminuria in 1836 with the paper "Cases and Observations Illustrative of Renal Diseases Accompanied with the Secretion of Albuminous Urine" [2, 3].

The point of this brief historic review, if there is one, is that the meaning of a word can change, and that the meaning of albuminuria has changed as the methods to detect and characterize proteins have evolved. Interestingly, the word proteinuria was introduced later, but the words albuminuria and proteinuria have often been used interchangeably—which clearly they are not.

Key words: proteinuria, albuminuria, glomerular filtration, tubular reabsorption.

Plasma albumin

Human albumin is coded in the q11-q22 region of chromosome 4, and circulates as a carbohydrate-free polypeptide chain of 585 amino acids, cross linked by 17 disulphide bonds, molecular mass 66,439 [1]. The disulphides are positioned in a repeating series of nine loop-link-loop structures centered around eight sequential Cys-Cys pairs. X-ray crystallography shows the molecule has a basic shape, somewhat romantically described as "heart shaped" [4]. However, the molecule can change form rapidly. This flexibility has been attributed to its loop-link-loop structure. Hence, albumin, as with many other proteins in solution, is not in a "platonic" state, but is a "kicking and screaming stochastic molecule" [1].

Genetic variants of albumin are very rare. Bisalbuminemia with heterozygosity of normal and variant alleles is the most common, and analbuminemia, a complete lack of circulating albumin, is extraordinarily rare and associated with mild edema, hyperlipidemia, and susceptibility to carcinogens and other toxins [1].

Albumin is characterized by its ability to bind to a wide variety of molecules, with "scavenger-like traits" making it a "haven for wanted and unwanted ligands" [1]. Relevant to vascular disease, fatty acid binding by albumin is an important factor in maintaining blood lipid levels. Some prostanoids (PG-D_2 and PG-E_2) are inactivated, while others (leukotriene A4 and thromboxane A2) are stabilized by binding to albumin [1]. Scavenging of reactive oxygen species (ROS) is another vasculoprotective role of albumin [5]. Other ligands include bilirubin, calcium, hormones, and a variety of drugs, including aspirin and warfarin. Prolonged uremia significantly alters the ligand-binding properties of albumin, and albumin contributes to whole blood acid-base buffering capacity. Constituting 60% of total plasma protein, and with low molecular weight, albumin contributes about 80% of the colloid osmotic pressure.

In tissue culture, albumin is a requisite environmental molecule, perhaps because of ROS scavenging [5]. In capillaries, albumin with other factors, especially orosomucoid, has been demonstrated to be necessary for maintenance of glomerular permselectivity [6], though this seems not to be the case in Nagase analbuminemic rats [7].

Renal handling of albumin

Though there is still controversy regarding the mechanism [4, 8], a variety of studies in normal rats and man indicate that some albumin does pass through the glomerular filtration barrier; conservatively 0.1 to 0.6 mg/dL or 150 to 800 mg/day in man (reviewed in [9]), although others have suggested the amount may be much greater [4]. Whether filtered albumin differs qualitatively from nonfiltered is unknown. The majority of this albumin is resorbed by proximal tubular cells, where receptors, particularly megalin and cubulin, deliver the albumin to the vacuolar lysosomal system, where an injurious cascade can be initiated [10, 11].

This process was once believed to result in total breakdown to amino acids, which were then delivered to the circulation. However, recently it has been shown that when tritium-labeled albumin is injected into humans, the majority of tritium-labeled peptides in the urine are low molecular weight (<10,000 daltons). It has been proposed that these fragments represent lysosomal products regurgitated to the tubular lumen [4].

Albumin in the urine

Small amounts of intact albumin are present in the urine of normal individuals (probably with the exception of genetic analbuminemics). Increased amounts of urinary intact albumin or its fragments can be a result of increased glomerular filtration, altered tubular resorption, or both. Albuminuria is a continuous variable, ranging from very little in the normal individual, to the massive amounts found in the nephrotic syndrome.

Consequent upon the structural flexibility and the ligand binding, circulating albumin exhibits chemical and physical microheterogeneity. It should be no surprise that by the time the albumin gets to the urine, even greater heterogeneity exists. The presence of albumin peptide fragments has been mentioned as one aspect of the heterogeneity of albumin-derived urinary products.

To complicate matters further it has recently been shown that all intact albumin molecules in the urine are not identified by immunoassays using antialbumin antibodies [4]. Using high-performance liquid chromatography (HPLC) to identify intact albumin molecules in diabetic urine, it has been demonstrated that the amount of albumin detected by HPLC exceeds that identifiable by radioimmunoassay. Some albumin molecules may have undergone steric modification or ligand binding such that the immunoreactive sites have become obscured.

When there is a large amount of albumin in the urine, this is of little practical concern because it will be detected by fairly nonspecific methods, such as precipitation or dye binding, as well as the highly specific immunoassays. In microalbuminuric states, however, there are small quantities of albumin and equivalent amounts of other proteins, such as Tamm Horsfall uromodulin. Here, the sensitivity and specificity of the assay and the molecule to be detected may become critical. Studies to date have shown the value of dipsticks, precipitation, and immunoassays to detect microalbuminuria. If microalbuminuria reflects changes occurring at the filtration membrane level, the evaluation of albumin in all three states (whole molecules, antibody-recognizable molecules, and peptide fragments) may be required. Whether these are of relevance to renal or vascular disease progression requires clarification.

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REFERENCES

1. Peters T, Jr: Serum albumin. *Adv Protein Chem* 37:161–245, 1985
2. Cameron JS, Hick SJ: The origins and development of the concept of a "nephrotic syndrome." *Am J Nephrol* 22:240–247, 2002
3. Cameron JS: The nephrotic syndrome: A historical review, in *The Nephrotic Syndrome*, edited by Cameron JS, Glassock RJ, New York, Dekker, 1988, pp 3–56
4. Russo LM, Bakris GL, Comper WD: Renal handling of albumin: A critical review of basic concepts and perspective. *Am J Kidney Dis* 39:899–919, 2002
5. Iglesias J, Abernetty VE, Wang Z, *et al*: Albumin is a major serum survival factor for renal tubular cells and macrophages through scavenging of ROS. *Am J Physiol* 277:F711–F722, 1999
6. Rippe B: What is the role of albumin in proteinuric glomerulonephritis. *Nephrol Dial Transplant* 19:1–5, 2004
7. Osicka TM, Strong KJ, Nikolic-Paterson DJ, *et al*: Renal processing of serum proteins in an albumin-deficient environment: An in vivo study of glomerulonephritis in the Nagase analbuminaemic rat. *Nephrol Dial Transplant* 19:320–328, 2004
8. D'amico G, Bazzi C: Pathophysiology of proteinuria. *Kidney Int* 63:809–825, 2003
9. Carlson JA, Harrington TJ: Laboratory evaluation of renal function, in *Diseases of the Kidney*, 5th ed, edited by Schrier RW, Gottschalk CW, Boston, Little, Brown and Conway, 1993, pp 361–405
10. Eddy AA: Proteinuria and interstitial injury. *Nephrol Dial Transplant* 19:277–281, 2004
11. Brunskill NJ: Pathophysiology of tubulointerstitial injury: Proximal tubular cell physiology and pathology. *Nephrol Dial Transplant* 15:S39–40, 2000